



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/47		A1		(11) International Publication Number: WO 98/06403					
				(43) International Publication Date: 19 February 1998 (19.02.98)					
(21) International Application Number: PCT/IB97/00983 (22) International Filing Date: 8 August 1997 (08.08.97) (30) Priority Data: 960100286 13 August 1996 (13.08.96) GR (71) Applicant (for all designated States except US): P.N. GEROLYMATOS S.A. [GR/GR]; 13 Asklipiou, GR-145 65 Kryoneri Attikis (GR). (72) Inventor; and (75) Inventor/Applicant (for US only): GEROLYMATOS, Panayotis, Nikolas [GR/GR]; 13 Asklipiou, GR-145 65 Kryoneri Attikis (GR). (74) Agents: BAGGER-SØRENSEN, Birgitte et al.; International Patent-Bureau, Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW. ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. With amended claims.						
(54) Title: USE OF THE CHELATING AGENT CLIOQUINOL FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF ALZHEIMER'S DISEASE									
<h2>Solubilisation of βAmyloid with Clioquinol</h2>									
Fraction	S	P	S	P	S	P	S	P	1-40
Clioquinol conc.		0		100%		10%		1%	
(57) Abstract The use of the chelating agent clioquinol for the manufacture of a pharmaceutical composition for the treatment of Alzheimer's disease is disclosed.									

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

USE OF THE CHELATING AGENT CLIOQUINOL FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF ALZHEIMER'S DISEASE

5 The present invention relates to the use of a chelating agent for the manufacture of a pharmaceutical composition for the treatment of Alzheimer's disease.

Alzheimer's disease is a chronic neurodegenerative disease prevalent primarily among elderly people.

10 The clinical diagnosis of Alzheimer's disease is supported by the existence and accumulation of amyloid deposits in the brain. The amyloid is primarily found in the terminal zones of neurons as morphologically heterogeneous deposits, also known as senile plaque.

15 The formation of senile plaque is related to the appearance of the symptoms and signs of the disease, including amnesia. After the formation of senile plaque, neurofibrillary tangles are produced in the neuronal bodies. The formation of neurofibrillary
20 tangles is related to the worsening of amnesia and of the other symptoms of dementia.

A major component of the amyloid deposits is a polypeptide referred to herein as $A\beta$ (Amyloid-beta). $A\beta$ is normally a soluble component of the cerebrospinal
25 fluid where it is found in concentrations of about 3-5 nM. $A\beta$ may have 39 to 43 amino acids, typically 40 amino acids, in the matured form and is derived as a proteolytic cleavage product from a cell surface protein called the amyloid precursor protein (APP)

30 (Kang et al. 1987). The normal function of $A\beta$ is not known at present but might be to form cation-selective channels across cell membranes (Kawahara et al., 1997).

The precipitation of synthetic $A\beta$ has been shown to be caused by several environmental factors including
35 low pH, high salt concentrations and the presence of metals, e.g. zinc, copper, and mercury (Bush et al.,

1995). It has been reported that A β itself specifically and saturable binds zinc of a high affinity binding (K_D = 107 nM) at a molar ratio of 1:1 (zinc: A β) (Bush et al., 1994a). This binding takes place at physiological concentrations of zinc (Bush et al., 1994b).

There is a strong supposition that the removal of amyloid deposits from patients suffering from Alzheimer's disease will alleviate the symptoms of Alzheimer's disease. Therefore, several attempts have been made to prepare a drug for the removal of amyloid deposits.

WO 93/10459 discloses a method for the treatment of Alzheimer's disease by administering a zinc binding agent. As preferred compounds phytic acid, desferri-oxamine, sodium citrate, EDTA, 1,2-diethyl-3-hydroxypyridin-4-one, and 1-hydroxyethyl-3-hydroxy-2-methylpyridin-4-one are mentioned.

DE 39 32 338 discloses the use of a chelator, such as 8-hydroxy-quinoline, for the treatment of Alzheimer's disease.

US 5373021 discloses disulfiram and its salts and analogues in as far as these can penetrate the blood-brain-barrier. The disclosed compounds may be used to reduce neurological damages caused by i.a. Alzheimer's disease.

The hitherto known compounds suggested for the treatment of Alzheimer's disease have several drawbacks, which has prevented their widespread use. E.g., most of the compounds are unable to penetrate the blood-brain-barrier and thus can hardly reach the areas in which the amyloid is deposited. Disulfiram, which may penetrate the blood-brain-barrier, has the drawback that it also is an alcohol deterrent.

The most extensively studied chelator is EDTA. However, the chelating effect of EDTA is relatively

weak towards zinc and copper. Furthermore, EDTA cannot penetrate the blood-brain-barrier and is considered relatively toxic.

The object of the present invention is to provide
5 a new use of a known pharmaceutical compound for the manufacture of a pharmaceutical composition for the treatment of Alzheimer's disease, said new compound having the ability to penetrate the blood-brain barrier, to effectively chelate heavy metals to prevent
10 the aggregation of amyloid, and to redissolve amyloid deposits. This object is achieved by using clioquinol for such a new use.

The term "treatment of Alzheimer's disease" used herein refers to the prevention, control and therapy of
15 Alzheimer's disease at any stage of its development.

Clioquinol has the chemical name 5-chloro-7-iodo-8-hydroxyquinoline and belongs to the group of hydroxyquinolines. Clioquinol has a known use as topical anti-infective agent. Especially, clioquinol has been used
20 for the treatment of amoebiasis and infectious diarrhoea. Clioquinol is only scarcely soluble in water within a pH range of 7-11. Outside this range suitable concentrations may be achieved.

The chelating ability of clioquinol is known for
25 Fe, Co, Ni and Zn (Kidani et al., 1974 and Tateishi et al., 1973). Using mass spectrophotometry the coordination number for clioquinol in case of Co(II), Ni(II), Cu(II) and Zn(II) is 2, whereas the coordination number for Fe(III) is 3. Reportedly, injected preparations of
30 clioquinol have crossed the blood-brain-barrier, leaving concentrations thereof in the brain in the order of 20 µl/ml when administrated at dosages of 10-20 mg/kg (Tateishi et al. 1975 and Tamura 1975). The concentration of clioquinol was also found to be high in

such areas of the brain like the hippocampus which is immediately affected by Alzheimer's disease.

Using microautoradiographic techniques, clioquinol has been shown in monkeys to form zinc chelates in the hippocampus. The Zn(II) chelates were mainly found in the terminal axodendritic boutons of the mossy fibres. Unconjugated clioquinol has an extremely rapid penetration when injected intravenously into the nervous system with practically no blood-brain-barrier (Shiraki, 1979).

Even though clioquinol had a known chelating and blood-brain-barrier penetrating ability it could not have been predicted that clioquinol also had the ability to redissolve zinc precipitated A β . According to the present invention the new use of clioquinol for the manufacture of a pharmaceutical composition for the treatment of Alzheimer's disease is based on this unexpected finding.

At present, it is believed that clioquinol and A β competitively chelate zinc and other heavy metals. Clioquinol is regarded as the strongest chelator and will, therefore, predominately capture the heavy metal ions. Thus, A β from precipitated zinc-A β will be resolubilized into the surrounding fluid because clioquinol will capture the zinc ions. The complex of clioquinol and zinc will penetrate the blood-brain-barrier and be cleared from the organism.

Since clioquinol is a relatively strong chelator, it may also chelate metal ions from enzymes or prosthetic groups. Therefore, it might be desirable to supplement trace metal ions or prosthetic groups to clioquinol treated patients, especially when establishing prolonged clioquinol treatments.

Vitamin B₁₂ contains cobalt. Previous case studies of subacute myelo-optic neuropathy (SMON) in Japanese

patients who were administrated clioquinol at higher dosages than recommended and for long periods indicate a connection between prolonged clioquinol treatment and vitamin B₁₂ deficiency. In the present application the interaction between clioquinol and B₁₂ is proved through *in vitro* and *in vivo* studies. Therefore, it may be beneficial to administrate vitamin B₁₂ together with or subsequent to the administration of clioquinol in order to prevent B₁₂ deficiency.

10 Clioquinol may be administrated in any appropriate amount in any suitable galenic formulation and following any regime of administration.

Preferably, the amount of daily administration will be from 10 mg to 750 mg clioquinol depending on the condition of the patient. A typically daily dosage is 100 mg. Alternatively, from 10 mg to 250 mg, preferable 100 mg clioquinol, three times daily, may be administrated. A daily dosage of up to 750 mg for a period of two weeks is considered without any risk of neurotoxicity or other side effects.

For the prevention of the onset of the symptoms and signs of Alzheimer's disease, or for the delay of the symptoms and signs in the evolution of the disease, daily clioquinol dosages of 10 mg to 100 mg can be administrated for long periods, viz. up to ten years.

The actual administrated amount is to be decided by the supervising physician and may depend on multiple factors, such as, the age, condition, file history, etc. of the patient in question. The results presented herein suggest that a "window" for the administrated amount of clioquinol exists, within which the best dissolving results are obtained. Such a window may be determined by the physician upon conducting routine experiments.

If clioquinol is going to be administrated for a prolonged period, clioquinol is preferably administered intermittently. In a first period clioquinol may be administrated e.g. for one to three weeks, 5 followed by a wash-out period, which may provide for restoration of any unwanted side effects of clioquinol. The duration of the wash-out period may be one to four weeks. During the wash-out period it is preferred to administrate B₁₂ and other prosthetic groups and/or 10 trace metals. After the wash-out period the first period may be repeated. The long-term intermittent therapy will provide not only for the resolubilisation of zinc-A β aggregates but also for the prophylactic inhibition of the formation of zinc-A β aggregates.

15 The intermittent administration of clioquinol will also reduce the toxicity potential of the drug, which means that the treatment may be extended throughout the evolution of the disease.

The pharmaceutical composition comprising clio- 20 quinol may be any suitable galenical formulation for enteral and parenteral administration aiming at delivering sufficient concentrations of clioquinol into the brain. It is preferred to administrate clioquinol as intravenous injections if it is desired to obtain high 25 brain concentrations rapidly. As it is more convenient to administrate a pharmaceutical composition orally, this way of administration may be used if it is not of importance to rapidly obtain high brain concentrations. The pharmaceutical composition may also be admini- 30 strated intradermally.

The pharmaceutical composition comprising clioquinol may comprise other active ingredients as well. Especially, the composition may contain trace metals or prosthetic groups such as vitamin B₁₂, and/or any other 35 therapeutic agent that can be used concurrently for the

treatment of Alzheimer's disease to improve or alleviate the symptoms and signs of Alzheimer's disease, or to delay the onset of any of the symptoms and signs of Alzheimer's disease. Alternatively, the other active
5 ingredient(s) may be administrated as separate pharmaceutical composition(s) together with the pharmaceutical composition comprising clioquinol.

According to the invention, the new use of clioquinol comprises:

- 10 1) the treatment of patients already diagnosed as having Alzheimer's disease at any clinical stage,
 - 2) the prevention of the disease in the patients with early or prodromal symptoms and signs, and/or
 - 3) the delay of the onset or evolution or aggravation or deterioration of the symptoms or signs of Alzheimer's disease.
-
- 15

In the following the present invention will be illustrated by means of examples, however, these examples are not to be considered as limiting for the
20 scope of the protection.

EXAMPLES

EXAMPLE 1

25

5.3 g of clioquinol was suspended with agitation in 200 ml of n-decane. The undissolved material was allowed to settle. Weighing the dried undissolved clioquinol after blowing off the decane indicated that
30 only 2% of the clioquinol dissolved in the decane. 100 ml of the (light yellow) supernatant was agitated together with 100 ml of PBS pH 7.4 and the phases allowed to separate. The PBS (lower phase) was collected and filtered to remove the residue which formed
35 at the phase interface upon extraction with the organic

solvent. Assuming that 2% of the clioquinol dissolved in the n-decane, and assuming that the partitioning coefficient is 1/1750 with PBS at 1:1 mixtures of decane/cliioquinol, the concentration of clioquinol in 5 the PBS is 800 nM.

Brain specimens were obtained for which a histopathological diagnosis of Alzheimer's disease was confirmed. Duplicate 0.5 g specimens of frontal lobe neocortex were homogenised in 3 ml of the clioquinol/ 10 PBS solution at 100%, 10% and 1% of the final PBS/cliioquinol extract and PBS alone.

The homogenates were centrifuged at 150,000 xg for thirty minutes and the supernatants collected and held on ice (fraction "S"). The pellets were subjected to an 15 identical homogenisation and centrifugation regime and the resulting supernatants again collected (fraction "P").

1 ml of each supernatant was treated with 200 μ l of ice cold 10% TCA to precipitate total protein including $A\beta$. The resulting pellet was washed once with 20 100% ethanol and resuspended in 100 μ l of TBS (tris 20 mM, NaCl 150 mM pH 7.4).

7.5 μ l of sample (S or P) was boiled for 5 min with an equal volume of tris-tricine sample buffer 25 containing 4% SDS and loaded onto a Novex pre-cast 10-20% tris-tricine gel followed by Western transfer onto nitrocellulose. Signal for $A\beta$ was detected using mAb WO2 (raised against residues 5-16 of $A\beta$) and visualized using ECL. The sensitivity of the detection system is 30 5-10 pg.

To validate the TCA precipitation for $A\beta$ 1 μ g of synthetic $A\beta$ 1-40 was added to 1 ml of PBS containing 10% BSA and the solution was treated as above. Signal for $A\beta$ was detected in the precipitated pellet but not 35 in the supernatant.

The result is indicated in fig. 1.

As it might be deduced from fig. 1, the clioquinol was effective in promoting the solubilisation of A β in the concentrations tested. Furthermore, the optimal 5 concentration was found to be "10%", indicating that one of the aggregation forms of A β , presumable the dimer, is more soluble in PBS than others.

While data are shown only for one specimen in fig. 1, data for 19 other specimens all indicate the same 10 tendency, viz. that clioquinol is effective in promoting the solubisation of A β .

Example 2

15 In this example the chelating ability of clioquinol and EDTA is compared.

Samples of 10 ng synthetic A β were placed in microtitre wells and caused to aggregate by the addition of 25 μ M ZnCl. The aggregates were then transferred to a 0.2 μ m nylon membrane by filtration. The 20 aggregates were washed with 200 μ l TBS alone, TBS containing 2 μ M EDTA, and TBS containing 2 μ M clioquinol. The membrane was fixed, probed with the anti-A β monoclonal antibody 6E10 and developed for exposure to 25 ECL-film. The transmittance of the ECL-film was measured and the relative signal strength calculated based on 100% for TBS alone. The relative signal strength was 66% for EDTA and 49% for clioquinol.

The results indicate that clioquinol is a better 30 chelator for zinc precipitated A β than EDTA.

EXAMPLE 3

In this example the resolubilising effect of 35 clioquinol is demonstrated.

A 2.5 μ M solution of A β in TBS at a pH of 7.4 was prepared. 95% of the A β was maintained in a soluble state. Addition of 30 μ M zinc resulted in precipitation of the soluble A β and only 43% was maintained in solution. The subsequent addition of 120 μ M clioquinol to the zinc precipitated A β resulted in an increase of soluble A β to 70%.

The results indicate that clioquinol is able to redissolve zinc precipitated A β .

10

EXAMPLE 4

In this example the influence of clioquinol on vitamin B₁₂ is studied in vitro using NMR spectroscopy.

15 Since clioquinol is practically insoluble in water within the pH range of 7-11, the study was conducted at pH 13. Three tubes were prepared. The first contained 1 mg clioquinol in 0.5 ml, the second contained 1.4 mg cyanocobalamine (B₁₂) in 0.5 ml, and the third contained 0.5 mg clioquinol + 0.7 mg cyanocobalamine in 0.5 ml (mol ratio 3:1).

20 The ¹H NMR spectra were recorded in a DRX 400 MHz spectrophotometer at 20°C. Comparison of the third spectra with the first and the second shows that some of the resonances of cyanocobalamine are shifted and the same is observed for two of the resonances of clioquinol. The results suggest an interaction between clioquinol and cyanocobalamine.

30 EXAMPLE 5

In this example the influence of clioquinol on vitamin B₁₂ is studied in vivo.

Six weeks old male mice were pre-treated with 35 clioquinol for three days (50mg/kg/day). The mice were

divided into two groups, a control group and a group which was injected with [^{57}Co]-cyanocobalamine. 48 hours after the injection the animals were sacrificed, and the brain, liver and kidney were dissected and 5 counted in a gamma-counter as thousand cpm/g tissue (wet weight) \pm SEM. The radioactivities in each of the groups are stated in Table 1 below:

Table 1

10	Treatment	Brain	Liver	Kidney
	Control	9.4 \pm 0.9	97 \pm 8	895 \pm 207
	[^{57}Co]-B ₁₂	8.4 \pm 1.5	85 \pm 21	252 \pm 61

A comparison of the results show that there were 15 no significant changes in the amount of radioactive accumulation in the brain and the liver. A reduction in the amount of vitamin B₁₂ trapped in the kidneys was apparent. It may be concluded that clioquinol has an influence on the concentration of B₁₂ in some of the 20 mice organs.

REFERENCES

- Kang et al. (1987) *Nature* 325: 733-736.
- Kirschner et al. (1987) *Proc. Natl. Acad. Sci.* 267:
5 6953-6957.
- Kawahara M.; Arispe N.; Kuroda Y.; Rojas E. (1997)
Biophysical Journal 73/1, 67-75.
- Bush, A.I., Moir, R.D., Rosenkranz, K.M., and
Tanzi, R.E. (1995) *Science* 268: 1921-1923.
- 10 Bush, A.I., Pettingell Jr., W.H., Paradis, M.D., and
Tanzi, R.E. (1994a) *J. Biol. Chem.* 269: 12152-
12158.
- Bush, A.I., Pettingell Jr., W.H., Multhaup, G., Para-
dis, M.D., Vonsattel, J.P., Gusella, J.F., Beyre-
15 uther, K., Masters, C.L., and Tanzi, R.E. (1994b)
Science 265: 1464-1467.
- Esler, W.P., Stimson, E.R., Jennings, J.M., Ghilardi,
J.R., Mantyh, P.W., and Maggio, J.E. (1996)
Neurochem. 66: 723-732.
- 20 Kidani Y et al., (1974) *Jap. Analyst* 23:1375-1378
- Tateishi J etl., (1973) *Psychiat. Neurol. Jap.* 75:
187-196.
- Shirilogi H., et al., (1979) *Handbook of Clinical
Neurology*, North Holland Publishing Company, 141-198.
- 25 Tamura Z, (1975), *Jap. J. med. Sci.Biol. Suppl* 28: 69-
77.

P A T E N T C L A I M S

1. Use of clioquinol for the manufacture of a pharmaceutical composition for the treatment of Alzheimer's disease.

5 2. Use according to claim 1, wherein the clioquinol is administrated in an amount of 10 to 250 mg one to three times daily.

3. Use according to claim 1 or 2, wherein trace metals and/or prosthetic groups are administrated
10 together with or subsequent to the administration of clioquinol.

4. Use according to claim 3, wherein the prosthetic group is vitamin B₁₂.

5. Use according to any of the proceeding claims,
15 wherein the pharmaceutical composition comprising clioquinol is administrated intermittently.

6. Use according to claim 5, wherein the pharmaceutical composition comprising clioquinol is administrated for one to three weeks followed by a
20 wash-out period of one to four weeks.

7. Use according to claim 6, wherein trace metals and/or prosthetic groups are administrated during the wash out period.

8. Use according to claim 7, wherein the prosthetic
25 ic group is vitamin B₁₂.

9. Use according to any of the preceding claims, wherein treatment is extended up to ten years.

10. Use according to any of the preceding claims, wherein the pharmaceutical composition comprising
30 clioquinol is formulated for oral administration.

11. Use according to any of the claims 1 to 9, wherein the pharmaceutical composition is formulated for parenteral administration.

12. Use according to any of the claims 1 to 9,
wherein the pharmaceutical composition is formulated
for intradermal administration.

AMENDED CLAIMS

[received by the International Bureau on 15 January 1998 (15.01.98);
new claims 13 and 14 added; remaining claims unchanged (1 page)]

12. Use according to any of the claims 1 to 9,
wherein the pharmaceutical composition is formulated
for intradermal administration.

5 13. Pharmaceutical composition comprising clio-
quinol and vitamin B₁₂.

14. Pharmaceutical composition according to claim
13, wherein the amount of clioquinol is 10 to 250 mg.

1/1

Solubilisation of β Amyloid with Clioquinol

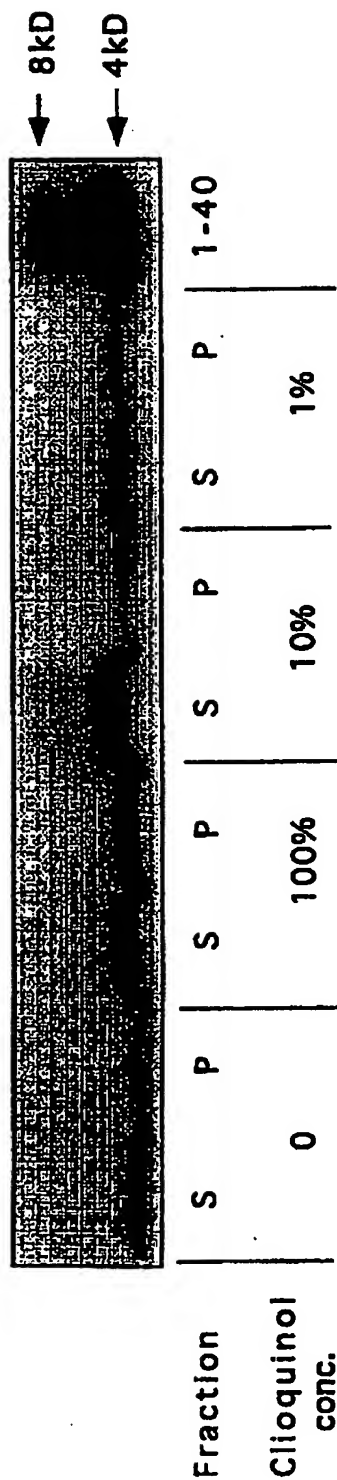


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/00983

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 10459 A (UNIV MELBOURNE) 27 May 1993 cited in the application see abstract see page 6, line 13 - page 11, line 9; claims 15-21 ---	1-12
A	DE 39 32 338 A (NMI NATURWISSENSCHAFTL U MEDIZ) 11 April 1991 cited in the application see the whole document ---	1-12
A	H. TJÄLVE: "THE ETIOLOGY OF SMON MAY INVOLVE AN INTERACTION BETWEEN CLIOQUINOL AND ENVIRONMENTAL METALS" MEDICAL HYPOTHESES, vol. 15, 1984, pages 293-299, XP002047206 see the whole document ---	1-12
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 November 1997

Date of mailing of the international search report

11/12/1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 97/00983

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A.I. BUSH ET AL.: "MODULATION OF ABETA ADHESIVENESS AND SECRETASE SITE CLEAVAGE BY ZINC" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, 1994, pages 12152-12158, XP002047207 cited in the application see the whole document ---	1-12
A	J.E.F. REYNOLDS: "MARTINDALE, THE EXTRA PHARMACOPOEIA" 1993, THE PHARMACEUTICAL PRESS, LONDON XP002047208 " Clloquinol " see page 511 ---	1-12
A	WO 95 31199 A (GEROLYMATOS P N SA ;LEGAKIS NICOLAOS (GR)) 23 November 1995 see abstract; claims -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/00983

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9310459 A	27-05-93	AU 669493 B CA 2123211 A EP 0613560 A JP 7503316 T	13-06-96 27-05-93 07-09-94 06-04-95
DE 3932338 A	11-04-91	NONE	
WO 9531199 A	23-11-95	AU 6580494 A EP 0713392 A	05-12-95 29-05-96

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.